Evaluation of Quality of Life and Disability in Patients with Hereditary Transthyretin-Mediated (hATTR) Amyloidosis with Polyneuropathy Following Treatment with Patisiran, an Investigational RNAi Therapeutic: Results from the Phase 3 APOLLO Study

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Hereditary ATTR (hATTR) Amyloidosis

Disease Overview and Introduction to Patisiran, an Investigational RNAi Therapeutic

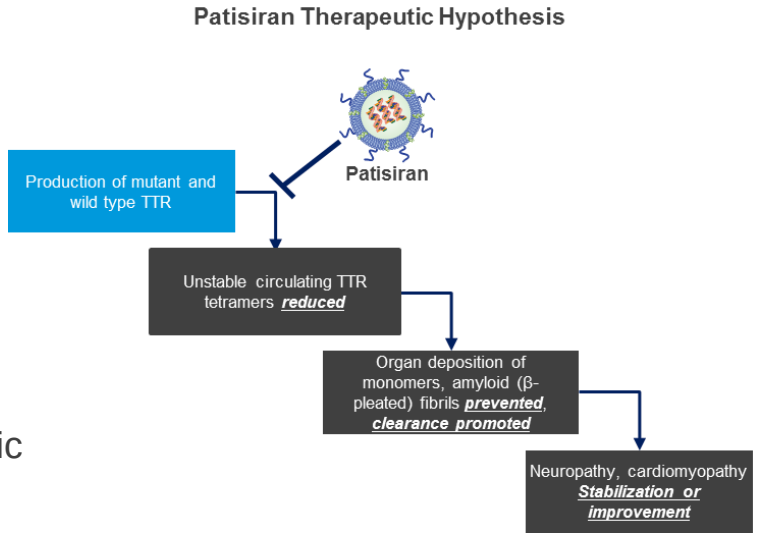
- **hATTR Amyloidosis**
  - Rare, inherited, rapidly progressive, debilitating, life-threatening, often fatal disease caused by mutations in transthyretin (TTR) gene resulting in misfolded TTR protein accumulating as amyloid fibrils in nerves, heart, and gastrointestinal tract[1-5]
  - Median survival 4.7 years following diagnosis[6]; reduced survival (3.4 years) for patients presenting with cardiomyopathy[6-8]

- Multisystem disease with heterogeneous clinical presentation that includes sensory and motor, autonomic and cardiac symptoms[2,9,10]
  - Disease continuum includes patients who present with predominantly polyneuropathy symptoms (formerly FAP) or cardiomyopathy symptoms (formerly FAC), yet many patients experience a variety of symptoms
    - Clinical manifestations (e.g., disease penetrance and rate of progression) is influenced by TTR genotype and geographical region

- Limited treatment options
  - Liver transplant for early-stage disease and TTR tetramer stabilizers
    - Tafamidis approved in EU for Stage 1 hATTR amyloidosis[11] and certain other countries outside U.S.
    - Diflunisal (generic NSAID) showed positive Phase 3 data in NIH-sponsored study[12]

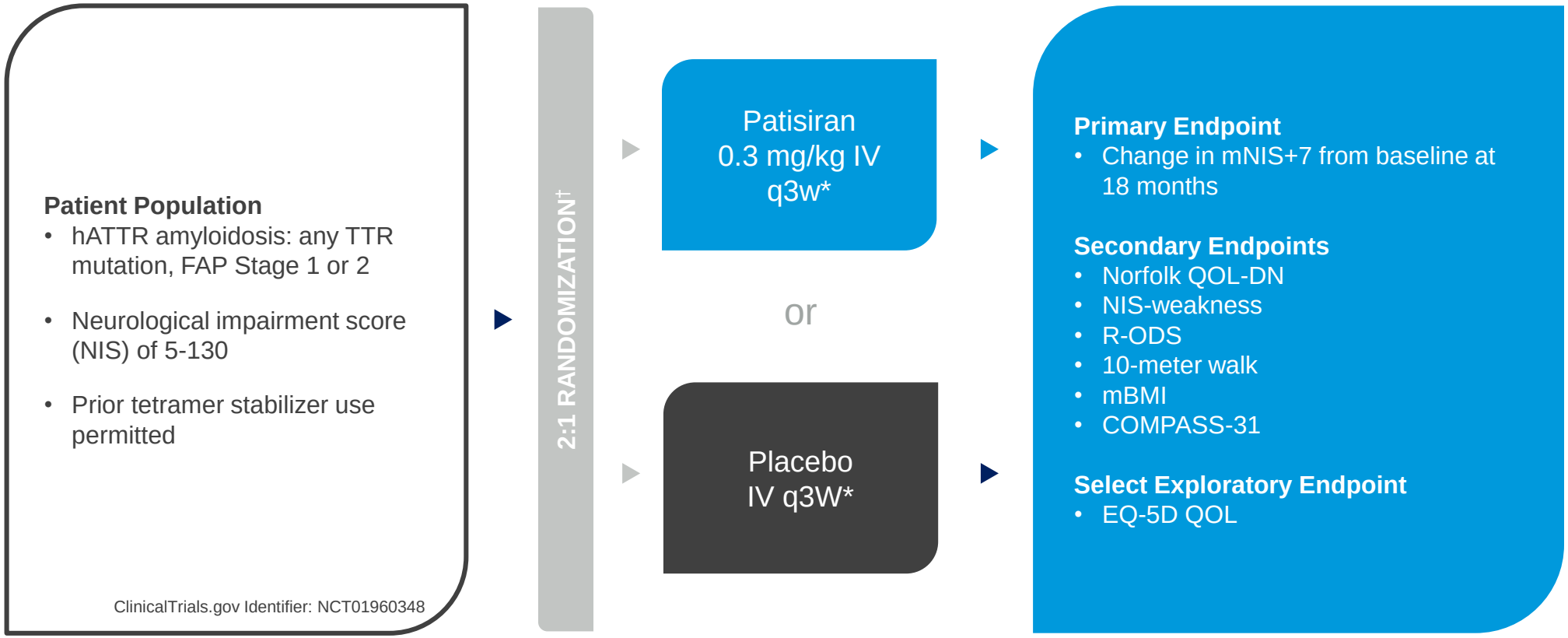
- Continued high unmet medical need for novel therapeutics

- **Patisiran, an Investigational RNAi Therapeutic**
  - Lipid nanoparticle formulated RNAi, administered by IV infusion, targeting hepatic production of mutant and wild-type TTR



1. Hanna M. Curr Heart Fail Rep. 2014;11(1):50-57; 2. Mohty D et al. Arch Cardiovasc Dis. 2013;106(10):528-540; 3. Adams D et al. Neurology. 2015;85(8):675-682; 4. Damy T et al. J Cardiovasc Transl Res. 2015;8(2):117-127; 5. Hawkins PN et al. Ann Med. 2015;47(8):625-638; 6. Swiecicki PL et al. Amyloid 2015;22(2):123-31; 7. Sattianayagam AJ et al. Eur Heart J 2012;33;1120–7; 8. Gertz MA et al. Mayo Clin Proc 1992;67(5):428-40; 9. Conceição I et al. J Peripher Nerv Syst. 2016;21(1):5-9; 10. Shin SC et al. Mt Sinai J Med. 2012;79(6):733-748; 11. Coelho T et al. Neurology. 2012;79:785-92; 12. Berk JL et al. JAMA. 2013;310:2658-67

Patisiran Phase 3 APOLLO Study Design



†Stratification factors for randomization include: neuropathy impairment score (NIS: < 50 vs. ≥ 50), early onset V30M (< 50 years of age at onset) vs. all other mutations (including late onset V30M), and previous tetramer stabilizer use (tafamidis or diflunisal) vs. no previous tetramer stabilizer use

*To reduce likelihood of infusion-related reactions, patients receive following premedication or equivalent at least 60 min before each study drug infusion: dexamethasone; oral acetaminophen/paracetamol; H2 blocker (e.g., ranitidine or famotidine); and H1 blocker (e.g., diphenhydramine).

Patients who completed study were eligible for patisiran treatment on Global OLE Study (NCT02510261)

COMPASS-31, composite autonomic symptom score-31; EQ-5D-5L, EuroQoL 5 dimensions-5L; mBMI, modified body mass index; mNIS+7, modified neuropathy impairment scale +7; Norfolk QOL-DN, Norfolk quality of life-diabetic neuropathy questionnaire; OLE, open-label extension; q3W, every 3 weeks; R-ODS; Rasch-built overall disability scale

Adams D et al. BMC Neurol 2017;17(1):181

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Patisiran Phase 3 APOLLO Study Endpoints

Primary Endpoints

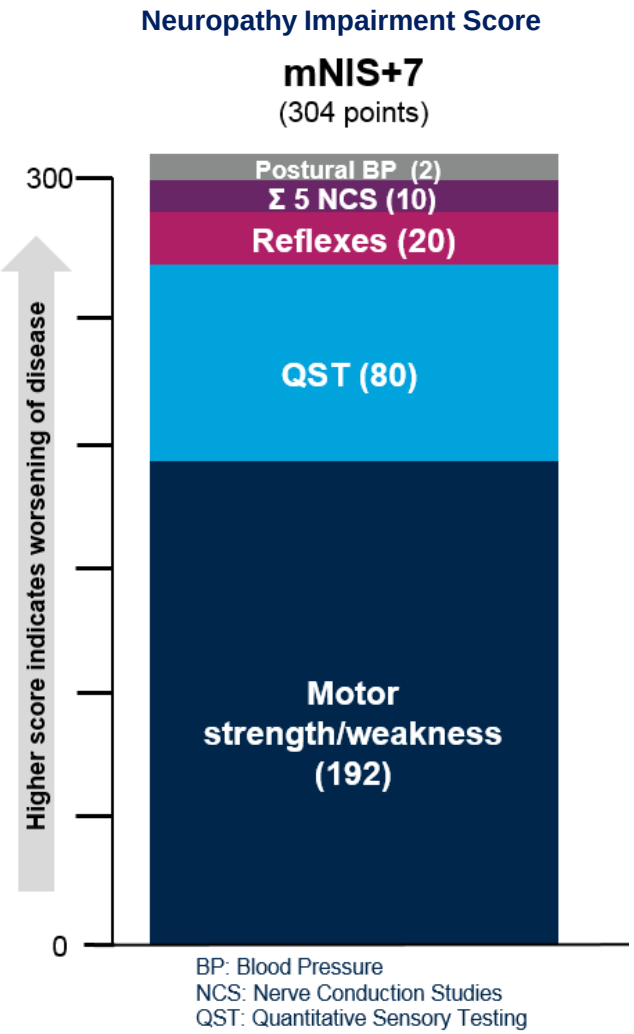
- **mNIS+7:** a composite measure of neurological impairment
  - Higher score indicates worsening of neuropathy

Select Secondary Endpoints

- **Norfolk QOL-DN:** 35-item QOL questionnaire that is sensitive to small fiber, large fiber, and autonomic nerve function
  - Higher score indicates worsening of QOL
- **R-ODS:** 24-item questionnaire used to capture activity and social participation (disability)
  - Lower score indicates worsening disability
- **10-meter walk test (m/sec):** assessment of ambulation that measures gait speed
  - Lower score indicates worsening
- **COMPASS 31:** 31-item questionnaire used to evaluate patient reported autonomic neuropathy symptoms
  - Higher score indicates worsening of autonomic neuropathy symptoms

Select Exploratory Endpoints

- **EQ-5D-5L:** 5-item standardized instrument to measure quality of life
  - Lower score indicates worsening of QOL
- **EQ-VAS:** assessment of patient's own global impression of their overall health
  - Lower score indicates worsening of QOL



10-MWT, 10-meter walk test; COMPASS 31, composite autonomic symptom score 31; EQ-5D-5L, EuroQOL 5 dimensions-5L; EQ-VAS, EuroQOL-visual analogue scale; NIS: neuropathy impairment score; Norfolk QOL-DN; Norfolk quality of life – diabetic neuropathy questionnaire; QOL, quality of life; R-ODS; Rasch-built overall disability scale

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Patisiran Phase 3 APOLLO Study Results

Baseline Demographics and Disease Characteristics

Demographic, n (%)	Placebo (N=77)	Patisiran (N=148)
Median Age, years (range)	63 (34, 80)	62 (24, 83)
Gender, males	58 (75.3)	109 (73.6)
Race†		
Asian	**25 (32.5)**	27 (18.2)
Black/African or African American	1 (1.3)	4 (2.7%)
White/Caucasian	50 (64.9)	**113 (76.4)**
Region*		
North America	10 (13.0)	**37 (25.0)**
Western Europe	36 (46.8)	62 (41.9)
Rest of World	31 (40.3)	49 (33.1)
hATTR Diagnosis		
Years since hATTR diagnosis, mean (min, max)	2.60 (0.0, 16.5)	2.39 (0.0, 21.0)
TTR Genotype		
V30M	**40 (51.9)**	56 (37.8)
nonV30M‡	37 (48.1)	**92 (62.2)**
Previous tetramer stabilizer use	41 (53.2)	78 (52.7)

Disease Characteristics, n (%)	Placebo (N=77)	Patisiran (N=148)
NIS		
Mean (min, max)	57.0 (7.0, 125.5)	60.5 (6.0, 141.6)
<50	35 (45.5)	62 (41.9)
≥50 - <100	33 (42.9)	63 (42.6)
≥100	9 (11.7)	23 (15.5)
FAP Stage		
1: unimpaired ambulation	37 (48.1)	67 (45.3)
2: assistance with ambulation required	39 (50.6)	81 (54.7)
3: wheelchair bound or bedridden	1 (1.3)	0
PND Score		
I: preserved walking, sensory disturbances	20 (26.0)	36 (24.3)
II: impaired walking but can walk without stick or crutch	23 (29.9)	43 (29.1)
IIIa: walk with 1 stick or crutch	22 (28.6)	41 (27.7)
IIIb: walk with 2 sticks or crutches	11 (14.3)	28 (18.9)
IV: confined to wheelchair or bedridden	1 (1.3)	0
Cardiac Subpopulation♯	36 (46.8)	**90 (60.8)**

Blue, bolded text indicated >10% difference in either group

†Other, patisiran N=1 (0.7%); More than one race, patisiran N=2 (1.4%); missing N=1 each for placebo (1.3%) and patisiran (0.7%)

*North America: USA, CAN; Western Europe: DEU, ESP, FRA, GBR, ITA, NLD, PRT, SWE; Rest of world: Asia: JPN, KOR, TWN, Eastern Europe: BGR, CYP, TUR; Central & South America: MEX, ARG, BRA

‡Represents 38 different TTR mutations

♯Pre-specified cardiac subpopulation: patients with evidence of pre-existing cardiac amyloid involvement at baseline without confounding medical conditions (i.e., patients with baseline left ventricular [LV] wall thickness ≥ 1.3 cm and no aortic valve disease or hypertension in medical history)

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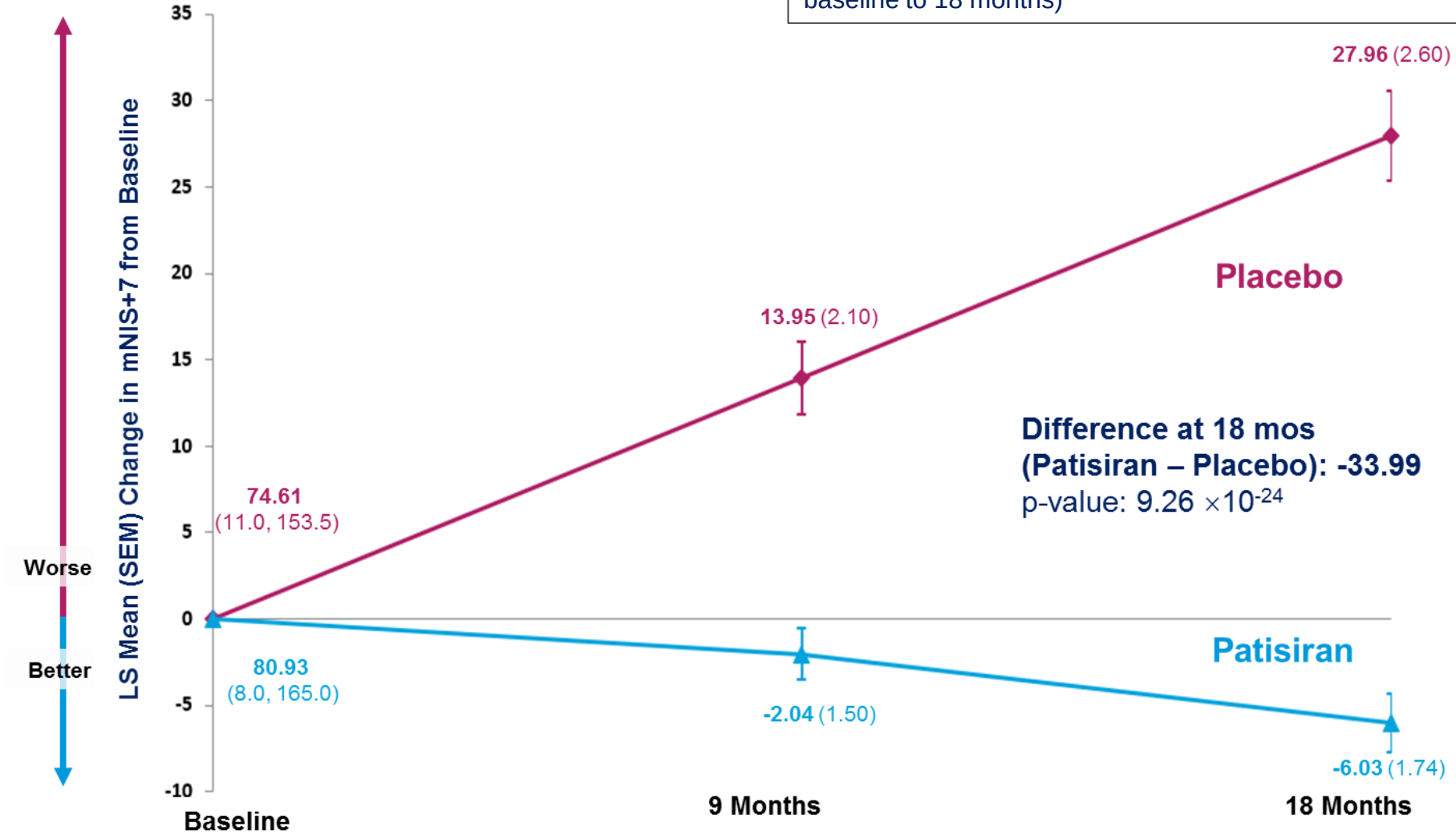
Patisiran Phase 3 APOLLO Study Results

mNIS+7: Change from Baseline

56.1% of patients in the patisiran group demonstrated improvement in mNIS+7 compared to 3.9% of patients on placebo
(Odds ratio: 39.9; p=1.82 x 10^{-15}; improvement defined as <0 point increase from baseline to 18 months)



MMRM, mixed-effects model repeated measures; mITT, modified intent to treat; mNIS+7, modified neuropathy impairment score + 7; LS, least squares; SEM, standard error of the mean
mNIS+7 reference range: 0-304 points

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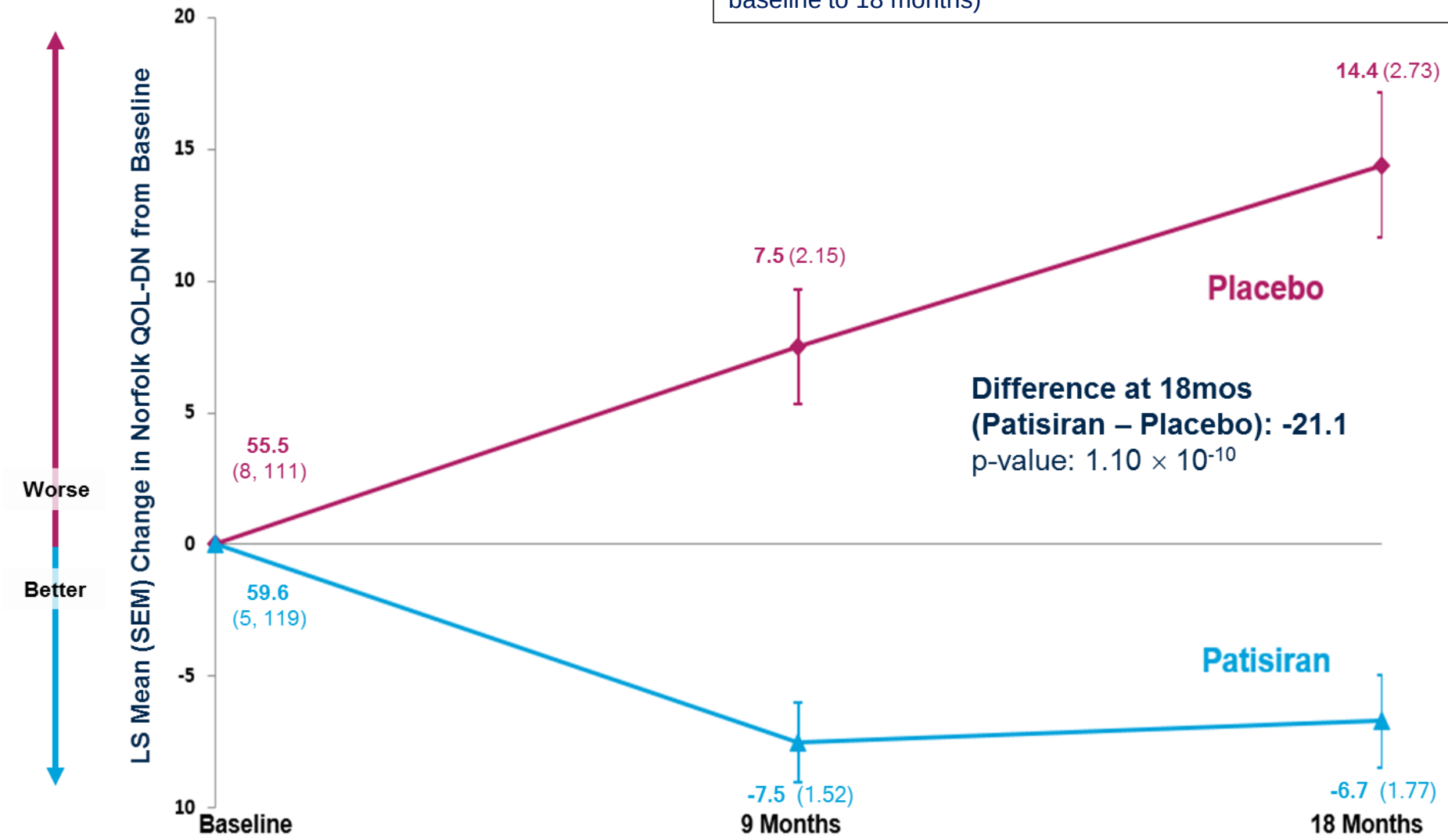
Patisiran Phase 3 APOLLO Study Results

Norfolk QOL-DN: Change from Baseline

51.4% of patients in the patisiran group demonstrated improvement in Norfolk QOL-DN compared to 10.4% of patients on placebo
(Odds ratio: 10.0; p=1.95 x 10^{-10}; improvement defined as <0 point increase from baseline to 18 months)



MMRM, mixed-effects model repeated measures; mITT, modified intent to treat; LS, least squares; Norfolk QOL-DN, Norfolk quality of life-diabetic neuropathy questionnaire; SEM, standard error of the mean
Norfolk QOL-DN reference range: -4 - 136

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Patisiran Phase 3 APOLLO Study Results

Norfolk QOL-DN: Change from Baseline in Individual Domains

- Patisiran demonstrated improvement across all domains of the Norfolk QOL-DN

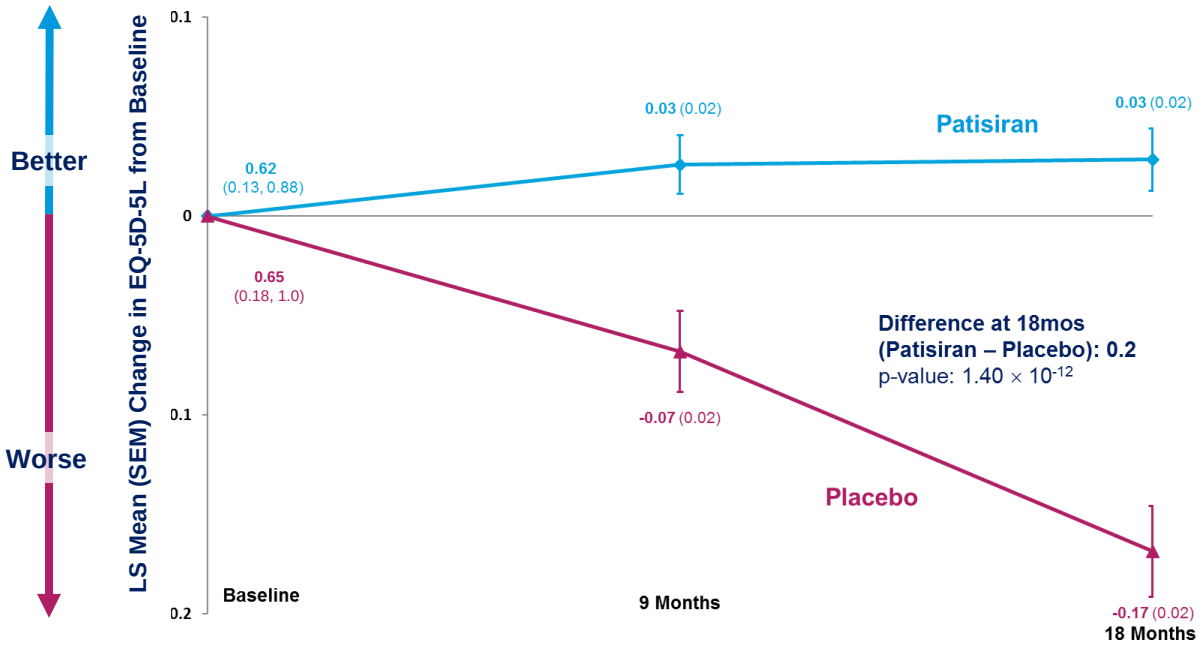
MMRM, mixed-effects model repeated measures; mITT, modified intent to treat ; Norfolk QOL-DN, Norfolk quality of life-diabetic neuropathy questionnaire

Patisiran Phase 3 APOLLO Study Results

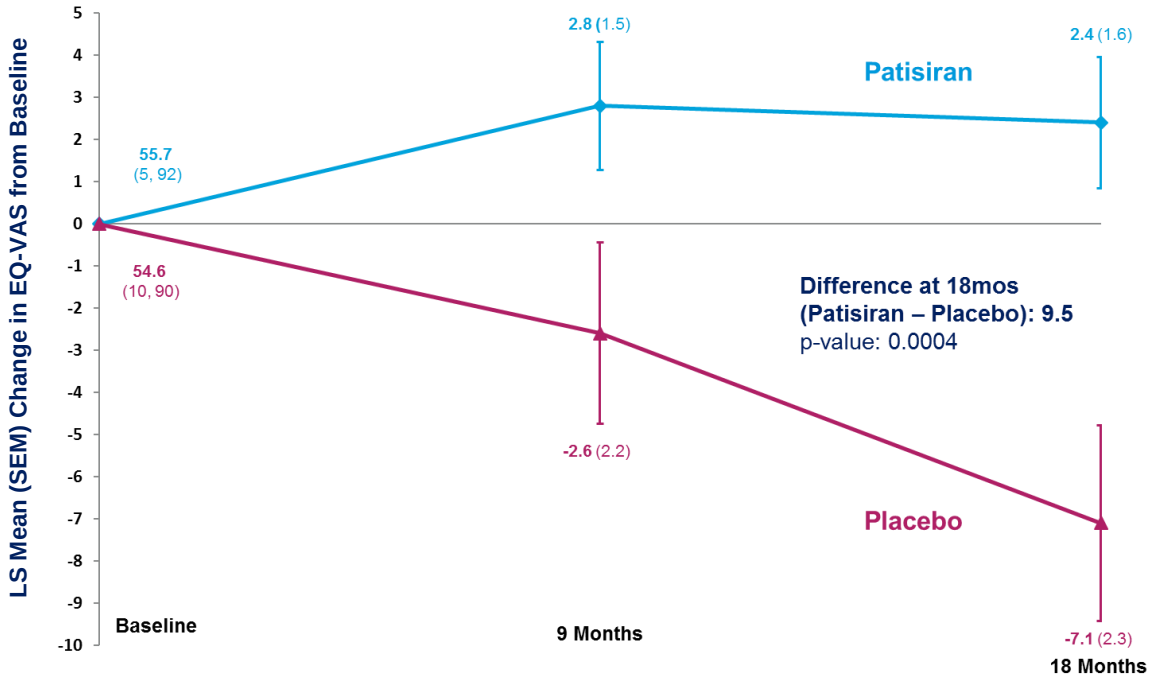
EQ-5D-5L and EQ-VAS: Change from Baseline

- Overall, patients in the patisiran group consistently improved their quality of life as measured by EQ-5D-5L and EQ-VAS compared with placebo at 18 months; this improvement was evident as early as 9 months

EQ-5D-5L



EQ-VAS



MMRM, mixed-effects model repeated measures; mITT, modified intent to treat; EQ-5D-5L; EuroQOL 5 dimension-5L; EQ-VAS, EuroQOL-visual analogue scale
EQ-5D-5L reference range: 0-1
EQ-VAS reference range: 0-100

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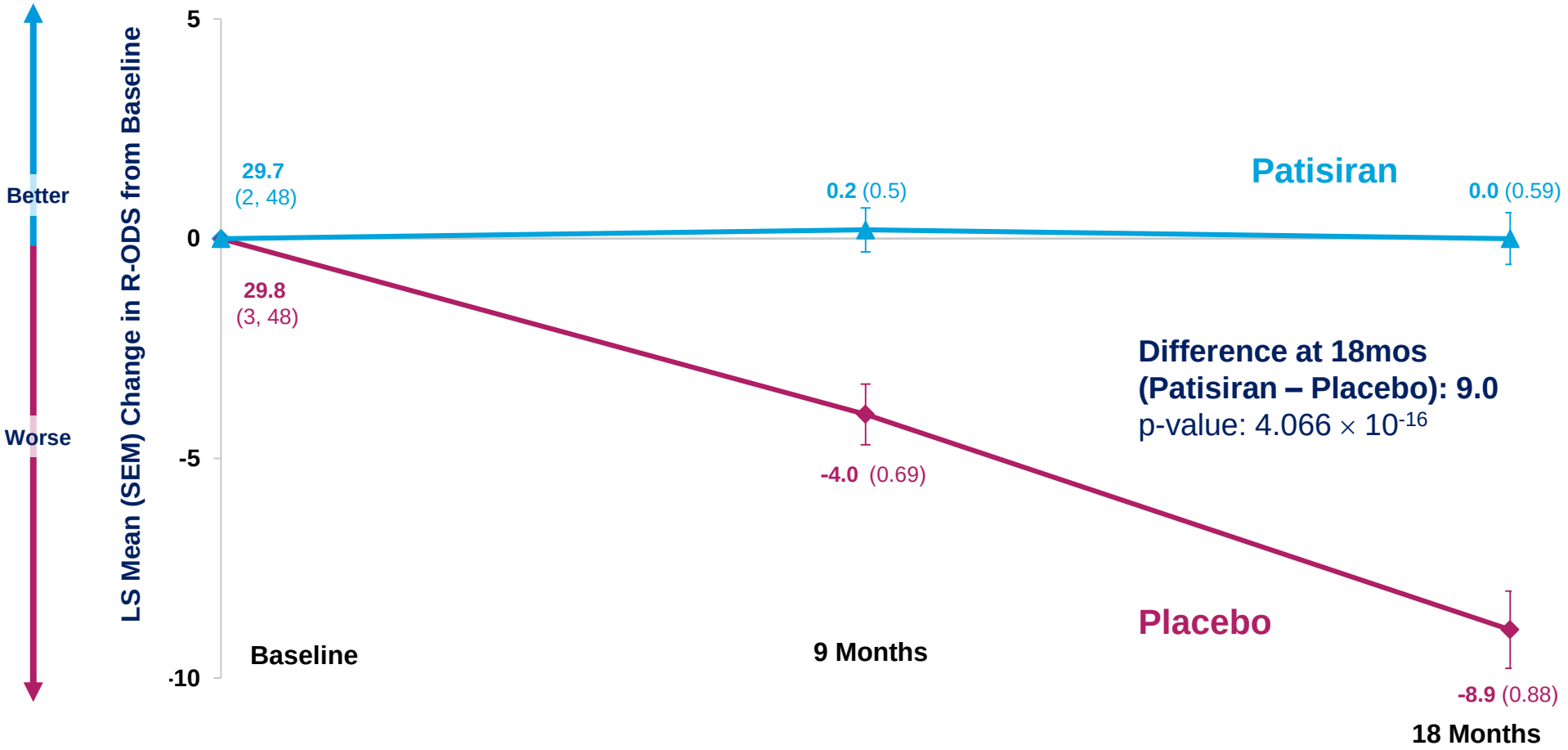
Patisiran Phase 3 APOLLO Study Results

R-ODS: Change from Baseline

- Patisiran demonstrated a significant improvement in disability at 18 months compared to placebo and nominal significance as early as 9 months

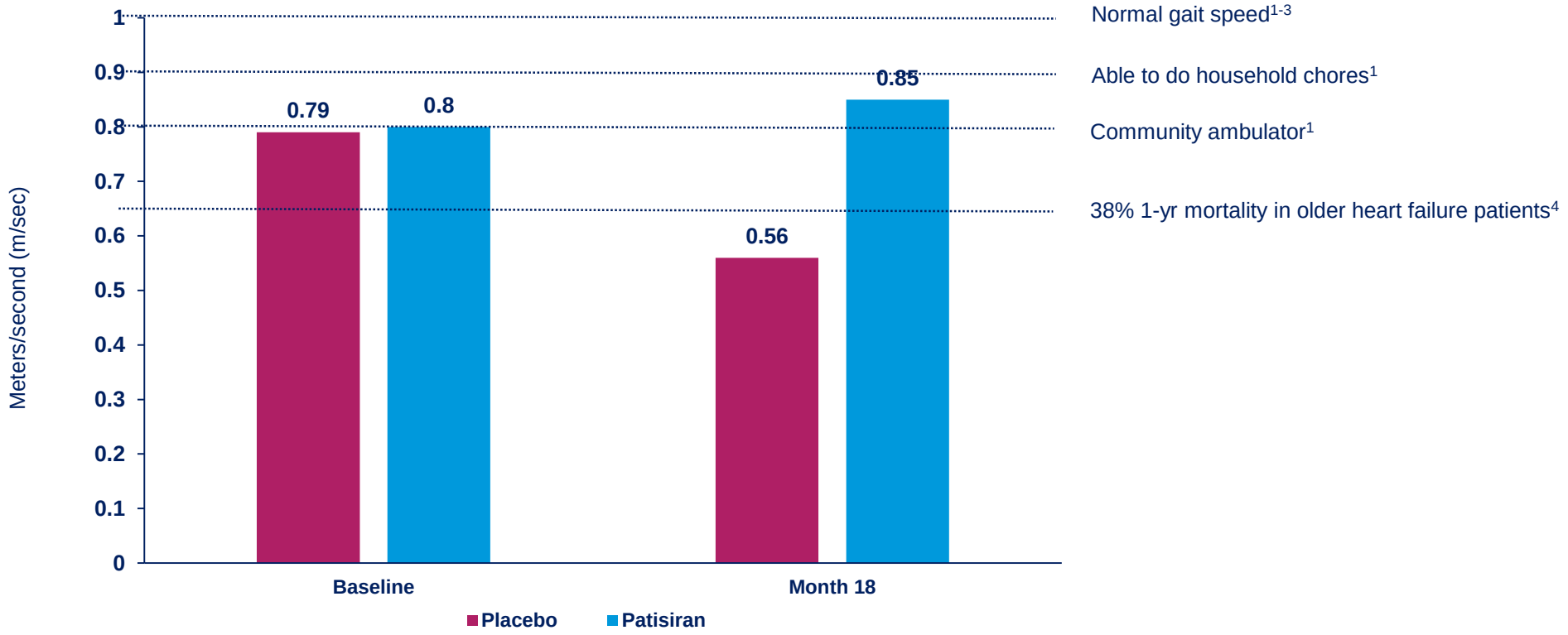


MMRM, mixed-effects model repeated measures; mITT, modified intent to treat; R-ODS, Rasch-built overall disability scale
R-ODS reference range: 0-48

Patisiran Phase 3 APOLLO Study Results

10-MWT: Change from Baseline to Month 18

- Patients in the patisiran group demonstrated a significant improvement in gait speed compared to placebo; this improvement in gait speed was evident as early as 9 months



Secondary endpoint; LS Mean		Placebo (N=77)	Patisiran (N=148)	Treatment Difference (Pati - PBO)	P-Value
10-MWT, m/sec	CFB to 18 mos	-0.24	0.08	0.311	1.88×10^{-12}

MMRM, mixed-effects model repeated measures; mITT, modified intent to treat; 10-MWT; 10-meter walk test; CFB, change from baseline; Pati, patisiran; PBO, placebo

1. Middleton A et al. J Aging Phys Act 2015;23:314-22; 2. Langlois JA et al. Am J Public Health 1997;87:393-397; 3. Bohannon RW. Age Ageing 1997;25:15-19; 4. Pulignano G et al. JACC Heart Fail 2016;4:289-98

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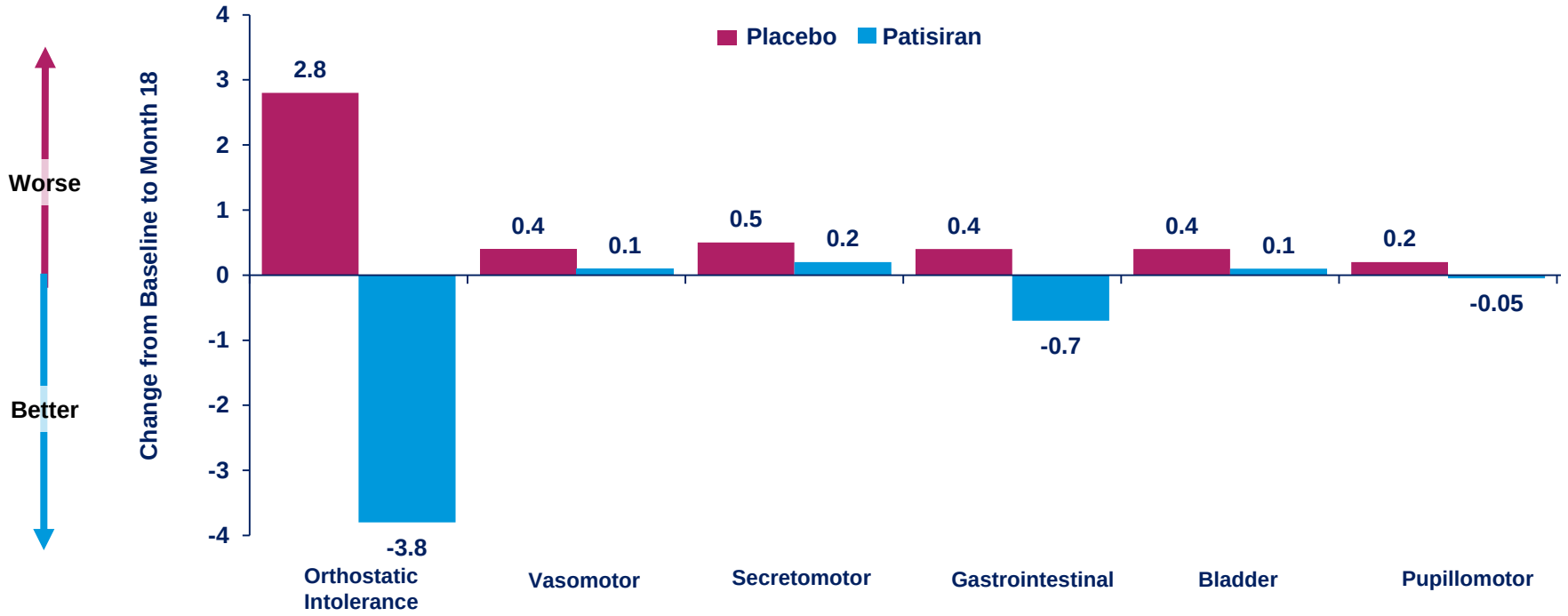
Patisiran Phase 3 APOLLO Study Results

COMPASS 31: Change from Baseline in Individual Domains

- Statistically significant improvement in autonomic neuropathy symptoms at 18 months for patients in the patisiran group compared to the placebo group



Secondary endpoint; LS Mean		Placebo (N=77)	Patisiran (N=148)	Treatment Difference (Pati - PBO)	P-Value
COMPASS 31	Baseline score, mean	30.31	30.61		
	CFB to 18 mos	**2.24**	**-5.29**	**-7.53**	**0.0008**

MMRM, mixed-effects model repeated measures; mITT, modified intent to treat ; CFB, change from baseline; COMPASS 31, composite autonomic symptom score 31
COMPASS 31 reference range: 0 - 100

Patisiran Phase 3 APOLLO Study Results

Safety and Tolerability

Type of Adverse Event, number of patients (%)	Placebo (N=77)	Patisiran (N=148)
Adverse event (AE)	75 (97.4)	143 (96.6)
Severe AE	28 (36.4)	42 (28.4)
Serious adverse event (SAE)	31 (40.3)	54 (36.5)
AE leading to treatment discontinuation	11 (14.3)	7 (4.7)
AE leading to study withdrawal	9 (11.7)	7 (4.7)
Death	6 (7.8)	7 (4.7)

Overall, 13 deaths in APOLLO study; no deaths considered related to study drug

- Causes of death (e.g., cardiovascular, infection) consistent with natural history; frequency of death trended lower in the patisiran group compared with placebo group

Majority of AEs were mild or moderate in severity

- Peripheral edema
  - Did not result in any treatment discontinuations and decreased over time
- Infusion-related reactions (IRRs)
  - Majority mild in severity that decreased over time; led to treatment discontinuation in 1 patient
  - No severe, life-threatening or serious IRRs

No safety signals regarding cataracts, hyperglycemia, infection, or osteopenia/osteoporosis

No safety signals regarding liver function tests, hematology including thrombocytopenia, or renal dysfunction related to patisiran

Safety in cardiac subpopulation comparable to overall study population

Adverse Events Occurring in ≥ 10% in Either Group

Preferred AE Term, number of patients (%)	Placebo (N=77)	Patisiran (N=148)
Diarrhea	29 (37.7)	55 (37.2)
Edema, peripheral	17 (22.1)	**44 (29.7)**
Infusion related reaction (IRR)	7 (9.1)	**28 (18.9)**
Fall	**22 (28.6)**	25 (16.9)
Constipation	13 (16.9)	22 (14.9)
Nausea	**16 (20.8)**	22 (14.9)
Dizziness	11 (14.3)	19 (12.8)
Urinary tract infection	**14 (18.2)**	19 (12.8)
Fatigue	8 (10.4)	18 (12.2)
Headache	9 (11.7)	16 (10.8)
Cough	9 (11.7)	15 (10.1)
Insomnia	7 (9.1)	15 (10.1)
Nasopharyngitis	6 (7.8)	15 (10.1)
Vomiting	8 (10.4)	15 (10.1)
Asthenia	9 (11.7)	14 (9.5)
Pain in Extremity	8 (10.4)	10 (6.8)
Muscular Weakness	**11 (14.3)**	5 (3.4)
Anemia	**8 (10.4)**	3 (2.0)
Syncope	**8 (10.4)**	3 (2.0)

Blue, bolded text: Indicates ≥5 percentage point difference in either group

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Patisiran Phase 3 APOLLO Study

Summary

hATTR amyloidosis is a multisystem, progressive, debilitating, life-threatening, often fatal disease with limited therapeutic options

Patisiran treatment resulted in significant improvement in polyneuropathy relative to placebo

- Benefits seen in motor, sensory and autonomic neuropathy
- Positive effects observed across wide range of disease severity and TTR genotypes, including patients with cardiac involvement

Treatment with patisiran resulted in an improvement in QOL compared to placebo; treatment with patisiran demonstrated favorable impact on disability compared to placebo

- Patisiran treatment led to an improvement in Norfolk QOL-DN as well as EQ-5D-5L and EQ-VAS
- Decrease in autonomic symptoms and improvement in gait speed in patisiran-treated patients, thus potentially lessening the burden of disease

Patisiran showed an encouraging safety and tolerability profile

- Frequency of deaths trended lower in the patisiran group versus placebo arm
- Key patisiran safety findings include mild to moderate peripheral edema and IRRs with only one treatment discontinuation due to these events
- No safety signals with regard to thrombocytopenia, hepatic or renal dysfunction

99% of eligible APOLLO patients enrolled into Global OLE study

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Acknowledgments

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